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Pharmacotherapy of Acute Coronary Syndromes: Medical Economics with an Emphasis on Clopidogrel

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Summary. **Acute coronary syndromes account worldwide for a significant burden of hospital- and societal costs. Pharmacotherapy of acute coronary syndromes consists of a combined antithrombotic therapy. Remarkable therapeutic advances have been made with the introduction of glycoprotein IIb/IIIa receptor inhibitors, low molecular weight heparins and thienopyridines, such as clopidogrel. Based on positive clinical data of large randomized trials numerous cost studies have been undertaken to analyse the cost-effectiveness of these new drugs. Most of them are showing an acceptable level of cost-effectiveness for the new treatments. Taking all available cost-studies into account, we conclude that new antithrombotic treatments are cost-effective as long as their use is limited to selected patient populations.**

Key Words. **acute coronary syndrome, cost-effectiveness, clopidogrel, acetyl salicylic acid**

Acute Coronary Syndrome: Burden of Disease

Acute coronary syndrome (ACS) is a term used to describe a spectrum of conditions associated with myocardial ischemia such as unstable angina (UA) and myocardial infarction (MI) (non-Q-wave, Q-wave and non-ST-segment elevation) [1]. Pathogenesis of ACS mainly results from arteriosclerosis of the coronary arteries and occlusive local thrombosis due to a ruptured plaque [2]. According to the World Health Organisation ischemic heart disease accounts for 12.6% of all deaths worldwide. In Europe the mortality rate of coronary artery disease (CAD) significantly varies in different countries with the highest rate in Eastern Europe. Although the mortality rate has been decreasing during the last years, the prevalence of patients with cardiovascular disease will increase due to an increased life expectancy.

In the past, several studies attempted to estimate the direct medical costs derived from treating ACS. In 1982 Charles et al. already published a paper analysing direct and indirect costs of medical and surgical treatment in patients with CAD [3].

Based on medical decision algorithms, Wittels et al. calculated expenses of different events resulting from CAD in the United States of America [4]. Charges were obtained from medical-care prices of different coronary care facilities. Average diagnosis- and treatment disbursements over a 5-year period, in 1986 prices, for acute MI were estimated at 51.211 US $ per patient, for angina pectoris 24.980 US $, UA 40.581 US $, sudden death 9078 US $ and non-sudden death 19.697 US $ respectively. Russell et al. used a *Markov-Model* to calculate direct medical costs in the USA [5]. Yearly total direct spending for diagnosis and treatment of patients with CAD in the USA was 16.2 billion US $ in 1995 prices. In Switzerland Sagmeister et al. attempted to analyse both direct and indirect medical costs (i.e. productivity losses) [6]. Total expenditures of ischemic heart disease in Switzerland in 1993 amounted to 2.1 billion CHF (1.45 billion US $). Indirect costs contributed approximately 47% to total costs. Expenses due to morbidity, disability and premature death were the major components of indirect costs. Direct costs were caused primarily by inpatient care, secondarily by outpatient care and only a low percentage by rehabilitation. Comparing the development of charges over a 5 year period (1988–1993) per patient, the authors concluded that spending for in- and outpatient treatment increased more than 50%, whereas indirect costs slightly decreased. This phenomenon is thought to be related to the introduction of novel, more effective diagnostic and therapeutic options that are more expensive but seem to result in a more favourable morbidity and lower mortality.

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Costs of Different Treatments for Acute Coronary Syndrome

The treatment of ACS consists of inpatient diagnosis and inpatient treatment usually done in an emergency room and intensive care unit and a long term secondary prophylaxis of the underlying condition, CAD. Therefore, efficacy of different treatments and their implication on costs have to be examined over a long time period. The cost perspective (hospital, society, country) is another important point. In each country there are different charges for drugs, medical procedures and hospitalisation; varying drug-costs may result in a more or less cost-effective ratio of a given treatment. Furthermore, not only direct medical costs, but also implications on indirect costs should be taken into account when measuring cost-effectiveness of treatments.

Brown et al. analysed the direct medical treatment costs for ACS in different countries in the initial hospitalisation phase as well as during subsequent hospitalisations for the same condition over a 6 month period [7]. They found differences in the following European countries due to levels of charges (Figure 1), but also to unequal utilisation rate of expensive cardiac arteriography and angioplasty.

Recommended pharmacological treatments targeting the thrombotic process in ACS include acetylsalicylic acid (ASA), glycoprotein IIb/IIIa-receptor (GPIIb/IIIa) inhibitors, thienopyridines and heparins [8]. The role of ASA in treatment of ACS is supported by abundant evidence and should be given as a standard treatment according to international guidelines [9]. Low treatment costs per patient and per day (0.04 US $) [10] and proven efficacy for ASA result in a very cost-effective ratio. The treatment of a whole population with daily ASA until death or over a 25 year period has an attractive cost-effectiveness of 11'000 US $ per quality-adjusted year of life gained (QALY) versus no secondary prophylaxis for patients with CAD [10].

GPIIb/IIIa- inhibitors are a new class of antithrombotic agents and are mainly used in addition to ASA in patients in whom a percutaneous coronary intervention is performed or in non ST-segment elevation MI. Efficacy has been documented in several large randomised controlled trials [11–19]. Based on data from these studies several modes were designed to analyse the cost-effectiveness (Table 1). Most of them show an economical advantage compared to other cardiovascular therapies. The cost-effectiveness studies are summarized in Table 1. As shown in this table, published cost-effectiveness data must be interpreted cautiously because of different follow up periods, different origins of cost data and different expressions of cost effectiveness (costs per life year gained, costs per prevented death of MI, costs per life years saved and incremental costs, etc.). Most of these studies were based on effectiveness data of the *PURSUIT* trial [16]. Generalizing these results to a whole population and applying the costs to different countries should be undertaken very cautiously. Nevertheless, research in the field of pharmacoeconomics is important in an area of development of new innovative but expensive therapies.

In conclusion, the efficacy and safety of GPIIb/IIIa inhibitors therapy as an adjunct of the treatment of non-ST-segment elevation ACS is widely accepted, based on large clinical data. In this class of antithrombotic agents costs remains a major issue. Acquisition costs of GPIIb/IIIa inhibitors are higher than the traditional agents (700–1700 US $ per infusion [20]), but cost-effectiveness data show that their incremental costs can be within the widely accepted ranges for new therapies. The main cost drivers of complications after ACS are the charges for rehospitalisation and revascularisation, that could be reduced with the addition of GPIIb/IIIa inhibitors to standard treatment. High acquisition expenses for this agents could be therefore offset by reduction of hospitalisations and treatment spending. However, there are several limitations

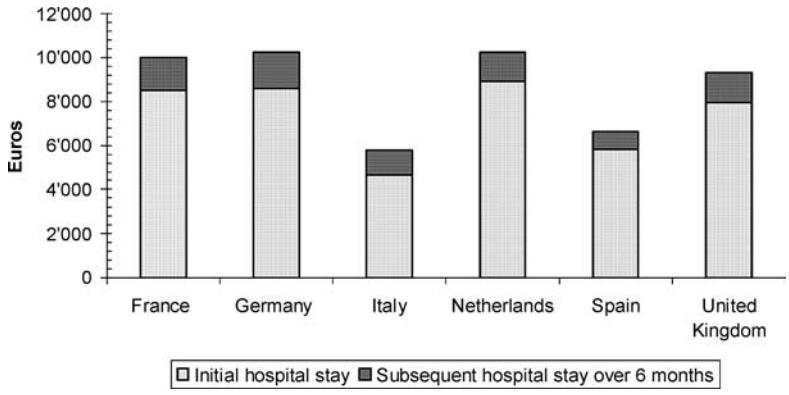

Fig. 1. *Average per patient initial- and subsequent hospital cost for the treatment of acute coronary syndrome*[7].

Table 1. *Cost-effectiveness studies in treatment of acute coronary syndrome with glycoprotein IIb/IIIa inhibitors*

Author, year	Country, currency	Drug	Calculated time period	Source of clinical data	Cost perspective	Cost-effectiveness ratio in €*
Hillegass, 1999 [20]	USA, US $	eptifibatide and tirofiban	30 days	PRISM, PRISM-PLUS, PURSUIT	Health care provider	32.000–82.000 per death or MI prevented
Mark, 2000 [21]	USA, US $	eptifibatide	6 months and lifetime	PURSUIT	Societal	16.491 LYG
McElwee, 1997 [22]	USA, US $	abciximab	Lifetime	IMPACT-II, EPIC,CAPTUE, GUSTO	Health care provider	20.000 LYG
Bell, 1999 [23]	USA, US $	abciximab, tirofiban, eptifibatide	30 days	PURSUIT, PRISM-PLUS,	Health care provider	40.000-46.000 per death or MI prevented
Szucs, 1999 [24]	Switzerland, CHF	tirofiban	7 days	PRISM-PLUS	Health care provider	366 saved per patient
Szucs, 2003 [25]	Germany, €	eptifibatide	7 days	PURSUIT	Health care provider	14.464 LYG
Brown, 2002 [7]	Germany, UK, France, Italy, Netherlands, Spain, €	eptifibatide	6 months	PURSUIT	Health care provider	7.285-13.742 LYG

LYG= life years gained.

*Converted to € based yearly discount rate of 3% and 2004 currency exchange rates.

Table 2. *Cost-effectiveness studies in treatment of acute coronary syndrome with Enoxaparin*

Author, year	Country currency	Source of clinical data	Cost perspective	Total savings per patient after 30 days in €*	Total saving per patient after 1 year in €*
Brosa, 2002 [28]	Spain, €	ESSENCE (TIMI 11B)	Health care provider	448	660
Mark DB, 1998 [29]	USA, US $	ESSENCE	Health care provider	1172	No data
O'Brien, 2000 [30]	Canada, US $	ESSENCE	Health care provider	No data	1485
Duteournay, 2000 [31]	France, €	ESSENCE	Health care provider	427	No data

*Converted to € based yearly discount rate of 3% and 2004 currency exchange rates.

to these studies. The time period chosen for the endpoints of the clinical studies (death and MI) is mostly limited to the hospitalisation time (7 days). The perspective of these cost-effectiveness studies is therefore limited to health care providers (hospital) and to direct medical costs. The long term socio-economic impact on the whole health care system of these new antithrombotic agents still has to be examined, as long term mortality, long term rehospitalisations and the associated indirect costs could significantly influence the cost-effectiveness of these drugs.

For heparins cost data mainly exist on cost-effectiveness of low molecular weight heparins (LMWH) versus the standard treatment with unfractionated heparin. Advantages of LMWH over unfractionated heparin include convenience of administration, higher bioavailability and the lack of need for monitoring. The most studied LMWH for ACS is enoxaparin, which was found to reduce the incidence of death, myocardial reinfarction and recurrent angina in patients with ACS compared with unfractionated heparin [26,27] (Table 2). Based on these trials, cost studies conducted in different countries suggest that enoxaparin is a less expensive treatment for the secondary prevention of ACS due to superior efficacy and lower total treatment and follow-up costs. The acquisition and administrative expenses of enoxaparin are higher than for unfractionated heparin. In Spain, for example, daily costs for enoxaparin treatment amount to 14.6 € compared to 0.64 € for unfractionated heparin [28]. But the reduced need for hospitalisation and revascularization over a period of 1 year amortises this initial difference in cost.

Clinical Profile of Clopidogrel

Clopidogrel, a thienopyridine antiplatelet agent, is an adenosine diphosphate (ADP)-receptor antagonist.

Table 3. *CURE (Clopidogrel in unstable angina to prevent recurrent events trial): Main results*

	ASA (n=6303)	ASA plus clopidogrel (n=6259)	Relative risk	P value
CV death, MI, stroke (primary end point) (%)	11.47	9.28	0.80	.00009
CV death (%)	5.49	5.06	0.92	NR
MI (%)	6.68	5.19	0.77	<.001
Stroke (%)	1.4	1.2	0.85	NR
Major bleeding (%)	2.7	3.6	1.34	.003

ASA= acetylsalicylic acid; CV = cardiovascular; NR = not reported.

Clopidogrel inhibits adenosine diphosphate (ADP) binding to its platelet receptor and subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thus inhibiting platelet aggregation. Clopidogrel irreversibly modifies the ADP receptor so platelets are affected for the remainder of their lifespan. An active metabolite is responsible for the drug's activity. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP. Doses of 75 mg per day inhibit platelet aggregation by 40 to 60% at steady state, which occurs within 3 to 7 days.

Cost-effectiveness studies for treatment of acute coronary syndrome with clopidogrel

In patients with ACS clopidogrel is recommended for acute as well as longer term treatment for at least 9–12 months [8]. Beyond this level of evidence, treatment will depend on the risk status of the patient and individual clinical judgement. Clopidogrel may be recommended for immediate and long-term therapy of patients who do not tolerate ASA, and is recommended for patients receiving a stent. Clopidogrel has shown its efficacy for patients with ACS, including also patients with medical treatment and angioplasty (with or without stent) or coronary artery bypass grafting. Clopidogrel has been shown to decrease the rate of the combined endpoint of cardiovascular death, MI, or stroke as well as the rate of the combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia [32].

CURE (Clopidogrel in Unstable angina to prevent Recurrent Events trial) was a study with 12.562 patients evaluating the efficacy and safety of the antiplatelet agent clopidogrel when administered with ASA in patients with ACS [32] (Table 3). This randomized trial studied the effectiveness and safety of clopidogrel in combination with ASA versus ASA alone when used for patients with non-ST-segment elevation ACS. The results indicate that the administration of clopidogrel in addition to ASA during a period of 3 to 12 months after an acute episode reduces the combined risk of cardiovascular death, MI, and stroke compared to ASA alone.

In *CURE*, clopidogrel when taken daily with ASA demonstrated a 20% ($P = 0.00009$) relative risk reduction in the combined end points of MI, stroke, or cardiovascular (CV) death with an absolute event rate of 9.3% in the clopidogrel group and 11.4% in the placebo group. The second primary outcome was a 14% ($P = 0.0005$) relative risk reduction in the combined end points of MI, stroke, CV death, or refractory ischemia, with an absolute event rate of 16.5% in the clopidogrel group and 18.8% in the placebo group.

Several economic studies addressed clopidogrel in ACS (Table 4).

Schleinitz et al. undertook a cost-utility analysis for high-risk acute coronary syndrome patients comparing combination therapy of clopidogrel and ASA for one year followed by ASA monotherapy with life long ASA therapy in patients presenting with unstable angina and electrographic changes or non-Q-wave myocardial infarction [33]. The collective treated with ASA alone, lived 9,51 QALYs after an initial event and generated costs were 127.700 US $. The addition of clopidogrel increased life expectancy to 9,61 QALYs and cost 129.300 US $ compared to ASA alone. The QALY for clopidogrel in combination to ASA compared to ASA monotherapy resulted in 15.400 US $. The investigators showed robustness to all sensitivity analyses for one year. For patients receiving longer combination therapy the treatment depends critically on the balance of thrombotic events, continuous efficacy and the increased bleeding risk of patients ingesting clopidogrel. In a probabilistic sensitivity analysis incremental cost-effectiveness ratios (ICERs) above 50.000 US $ were determined in less than 3% of all simulations. The authors noted that this investigation would not apply to patients presenting with severe heart failure or those undergoing short-term treatment with glycoprotein IIb/IIIa inhibitors. It would also not apply to patients who have recently undergone revascularisation in a patient population receiving long term anticoagulation. Schleinitz et al. proved that clopidogrel is cost-effective in addition to ASA given for one year, which is in the accepted range for patients with high-risk acute coronary syndrome. Life expectancy rose with combination therapy. The authors indicated that further trials should be performed comparing long-term period efficacy of clopidogrel in relation to bleeding risk before an extended therapy is established. Lamy et al. undertook an economic analysis of the use of clopidogrel in the UK, USA, Sweden, France and Canada based on the *CURE* study [34]. Their hypothesis was that clopidogrel is more expensive but also more effective than placebo. The group performed an incremental cost-effectiveness analysis, comparing the differences in costs and effectiveness between intervention and no intervention. The authors used the

Table 4. *Overview of cost-effectiveness studies of clopidogrel for treatment of acute coronary syndrome*

Author	Year publ.	Country	Calculated time period	Source of clinical data	Cost perspective	Cost effectiveness ratios in €*
Schleinitz et al. [33]	2005	USA	lifetime	CURE	societal	17.423 € per QALY
Lamy et al. [34]	2004	UK USA Sweden France Canada	9 months	CURE		16.847 € PPLE 25.437 € PPLE 13.857 € PPLE 16.186 € PPLE 5.585 € PPLE
Lindgren et al. [35]	2004	Sweden	12 months	CURE	societal	1.009–1.365 € per LYG
Latour-Perez [36]	2004	Spain	12 months	CURE		12.000 € per QALY
Frei [37]	2004	Switzerland	9 months	CURE		2.540 € per LYG
Brüggenjürgen [38]	2003	Germany	9 months	CURE		13.134–23.035 € PPLE
Schwarz [39]	2004	Austria	9 months	CURE		4.146 € per LYG

PPLE = per prevented life-threatening event; LYG = life years gained; QALY = quality-adjusted life years.
*Converted to € based yearly discount rate of 3% and 2005 currency exchange rates.

Table 5. *Overview of cost-effectiveness studies for secondary prevention of acute coronary syndrome*

Author	Year publ.	Country	Calculated time period	Source of clinical data	Cost perspective	Cost effectiveness ratios
Gaspoz [10]	2002	USA	25 years	Coronary Heart Disease Model		114'000 US $ QALY
Haldemann [42]	2001	Switzerland	1.9 years	CAPRIE		22837 CHF LYG
Schleinitz [43]	2004	USA	Life time treatment	CAPRIE		25100 US $ QALY

LYG = life years gained, QALY = quality-adjusted life years.

placebo collective result as proxy for no intervention. The costs included were direct medical care charges for drugs and hospitalisation. The *Cure* trial did neither contain data to account direct costs associated with testing or visits of outpatients nor indirect costs due to loss of productiveness. For Canada the investigators relied on a detailed case costing system to register all procedures, investigations and drugs at the specific length of stay in the study. For all other countries the DRG-system (diagnosis related groups) was used where all resources are merged in a single code. The average amount for each treatment group was calculated and reported in local currency for the corresponding country. For initial hospitalisation the average costs were reduced for the clopidogrel group in all countries while the follow up costs and finally the total costs were significantly higher with clopidogrel compared to placebo. Difference in costs (95% CI): UK 208 £ (119, 297); USA 451 US $ (58, 845); Sweden 2571 SKr (728, 4412); France 325 € (85, 565); Canada 161 CAN $ (−185, 506). With an absolute reduction of total primary events of 2.0% for clopidogrel an incremental cost-effectiveness (ICER) of 10.366 £ (UK), 22.484 US $ (USA), 127.951 SKr (Sweden), 16.186 € (France) and 7.973 CAN $ (Canada) resulted. Lamy et al. concluded that there is a favourable incremental cost effectiveness ratio (ICER) for clopidogrel compared to other medical therapies. Clopidogrel reduced the initial and subsequent hospitalisation expenses but the acquisition cost during the follow up phase resulted in an overall rise of direct costs. The duration of the therapy should be individualised depending on patients' profile, alternative therapy options and country-specific economic status.

The cost-effectiveness of clopidogrel in ACS was recently examined in Sweden by Lindgren et al. [35] The investigators attempted to evaluate the long-term cost-effectiveness of clopidogrel in addition to standard therapy (including ASA) in patients with ACS without ST-segment elevation. They aimed at evaluating the cost-effectiveness in terms of cost per life year gained (LYG) of clopidogrel treatment in Sweden. The incremental cost-effectiveness ratios (ICER) were assessed by using a *Markov model* with transition probabilities estimated from the *Swedish hospital discharge and death registers*. The patients were assumed to be treated for one year, with treatment effects and drug costs taken from the *CURE* trial.

They found an incremental cost-effectiveness ratio of 1.365 € per life year gained (*CURE* trial population including direct and indirect costs). For the population similar to the Swedish death register the ratio showed 1.009 €. The authors reasoned that adding clopidogrel to standard therapy including ASA is cost-effective in the studied setting and compares favourably with other cardiovascular treatment and prevention strategies.

Latour-Perez et al. established a cost model for cost-effectiveness of clopidogrel in non-ST-segmental elevation ACS in Spain over one year [36]. Based on the *Cure-* and the *Framingham* study a Markov decision tree was developed taking into account the Spanish age-specific mortality rates in the national public health system. Using national diagnosis related groups to reflect the costs of one year of treatment with clopidogrel the costs per quality adjusted life year gained (QALY) was 12.000 €. According to the established willingness to pay levels in Spain (6.000–12.000 €), the cost-effectiveness ratio for clopidogrel was shown to be within the accepted ranges. A sensitivity analysis showed costs per QALY ranging for a high-risk patient from 5.000 € to 30.000 € for a low risk case.

For Switzerland, Frei et al. calculated based on the *CURE* data 0.2 life years saving with clopidogrel treatment [37]. The ICER of clopidogrel and ASA over ASA alone were found to be CHF 3.810. The authors concluded a comparable cost-effectiveness profile compared to other cardiovascular therapies.

Brüggenjürgen et al. based their results on the German DRG-system (diagnosis related groups) [38]. In a DRG scenario the average total cost per patient came to 6.252 € for the clopidogrel group and to 5.789 € for placebo. The incremental costs efficacy ratios ranged form 13.134 € for a per diem remuneration to 23.035 € for DRG remuneration per prevented severe life-threatening event. In a 2004 base case analysis (2500 €) the costs in the clopidogrel group were 5.367 € as compared to 4.996 in the placebo group. The associated ICER was 18.458 € per life-threatening event avoided. The authors calculated an acceptable cost-effectiveness ratio for the German population, even for the most conservative scenario (anticipation of DRG-based remuneration).

For Austria Schwarz et al. predicted an incremental survival of 0,12 years in patients with acute coronary syndrome for 12 months treatment with clopidogrel on top of standard therapy [39]. Evaluation of direct and indirect disbursements indicated cost per life-year saved of 4.146 €, regarded as cost-effective from the Austrian societal view.

Cost-effectiveness studies for secondary prevention of cardiovascular events with clopidogrel

CAPRIE (Clopidogrel versus ASA in Patients at Risk of Ischemic Events) was a randomized, blinded, international trial designed to assess the relative efficacy and safety of clopidogrel (75 mg once daily) and ASA (325 mg once daily) in reducing the risk of ischemic stroke, MI, or vascular death in patients with recent MI, stroke, or established peripheral arterial disease [40]. *CAPRIE* studied patients that had known manifestations of thrombotic disease such as:

Recent MI [≤35 days] with chest pain ≥20 min, increased cardiac enzymes or ECG changes or recent ischemic stroke (≥1 week and ≤6 months) with neurological deficit of atherosclerotic origin, neurological signs persisting for ≥1 week, and CT or MRI to rule out haemorrhage or an established peripheral arterial disease (PAD) defined as either intermittent claudication of presumed atherosclerotic origin and ankle brachial index ≤0.85, or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty.

The results of the *CAPRIE* study, involving 19.185 patients, established clopidogrel as a potent platelet aggregation inhibitor in a broad group of patients at risk of atherothrombotic events. In *CAPRIE*, clopidogrel demonstrated an 8.7% ($P = 0.045$) overall risk reduction in the combined endpoint of first occurrence of MI, stroke, or other vascular death. In a subgroup of 4.496 high-risk patients, followed after a second cardiovascular event (CVE), the clopidogrel group showed a 14.9% lower relative risk of recurrent CVE than the patients in the ASA group [41]. The risk of a subsequent CVE was higher in patients who already had two CVEs, even if the second or third event was not necessarily the same like the first one. After one- and three- year follow-up, patients receiving clopidogrel were less likely than those receiving ASA to be hospitalised for a CVE or to die from a CVE. One year after their second event, 16.1% of the clopidogrel group and 18.5% of the ASA group had an ischemic stroke, MI, or repeat hospitalisation for CVE. The composite end point for an ischemic stroke, MI, or vascular death was reached in 8.8% of the clopidogrel-treated patients and in 10.2% of the ASA group [41]. Three years later, 32.7% of the clopidogrel patients and 36.6% of the ASA patients showed another CVE. Vascular death occurred in 20.4% of the clopidogrel patients and in 23.8% of the ASA group. Consequently, treating 29 very high-risk patients with clopidogrel would prevent one vascular death, MI, or ischemic stroke over three years.

The statistical significance favouring clopidogrel over ASA was marginal ($P = 0.045$, based on overall incidence of primary outcome events: 9.8% for clopidogrel versus 10.64% for ASA).

Gaspoz et al. investigated the cost-effectiveness of ASA and clopidogrel for secondary prevention in patients with an ACS [10] (Table 5). The incremental cost-effectiveness was estimated by using the *Coronary Heart Disease Policy Model* (tracks patients surviving the first month having coronary disease; categorizes patients of number, year, history of events and

assigns the annual cost on an individual basis). The authors performed a four-strategy scenario:

ASA for all eligible patients, ASA for all eligible patients plus clopidogrel for patients who were ineligible for ASA, clopidogrel for all patients and two options for the combination of ASA for all eligible patients plus clopidogrel for all patients. The cost-effectiveness ratio (25 years) for ASA was about 11.000 US $/QALY while clopidogrel showed costs of 114.000 US $/QALY. The authors concluded that the cost-effectiveness of clopidogrel is currently unattractive for secondary prevention of acute coronary syndrome, unless its use is restricted to patients who are ineligible to ASA or the price of clopidogrel would be reduced by 60 percent. However 25 years of treatment without any price reduction in case of patent lost and the expected long time period of compliance are questionable. In addition the chosen population model shows a much lower risk for the acute coronary syndrome than the population in *CURE*.

Haldemann et al. included the costs of ischemic strokes and primary non-fatal intracranial haemorrhages as well as MIs in their cost-effectiveness analysis of the CAPRIE trial (Table 5). They determined 1.5 million CHF net cost savings of treating 1000 patients, i.e. the incremental drug costs less the savings of adverse outcomes. Patients receiving clopidogrel gained 63 life years per 1000 patients as compared to ASA alone. They came to a justifiable economic perspective for the use of clopidogrel by additional yearly costs of 722 CHF per patient. Their analysis yield a cost-effectiveness of 24.164 CHF nominal and 22.837 CHF discounted per additional year of life saved.

Schleinitz et al. evaluated the cost-effectiveness of clopidogrel and ASA for secondary prevention in patients with a prior MI, stroke or peripheral arterial disease [43] (Table 5). They used a Markov model based analysis on the lifetime treatment of a 63-year-old patients. The event probabilities were derived from the *CAPRIE* trial. Outcome measures included costs, life expectancy in quality adjusted life-years (QALY's), incremental cost-effectiveness ratio (ICER) and events. For patients presenting with peripheral arterial disease, clopidogrel could increase the life expectancy by 0.55 QALY at an incremental cost-effectiveness ratio of 25.100 US $ per QALY, compared to ASA. In post stroke patients, clopidogrel showed an increase of life expectancy by 0.17 QALYs with a cost-utility ratio of 31.200 US $ per QALY. In post myocardial patients ASA appeared to be less expensive and more effective than clopidogrel. The authors pointed out that clopidogrel provides an increase in quality adjusted life expectancy and costs that are in line with the traditional societal limits for patients presenting either a peripheral arterial disease or a recent stroke. They could not show an increased efficacy for clopidogrel following MI compared to ASA, due to an increased rate of vascular death in clopidogrel treated patients in *CAPRIE*. In a larger cohort (post hoc analysis *CAPRIE*), clopidogrel was associated with a reduction in risk of 7.4%, suggesting that clopidogrel does remain cost-effective in patients that had a previous MI. For stroke patients clopidogrel had a more favourable price than ASA. The study is limited by the choice of events and interventions (no bypass patients, atrial bypass patients, percutaneous coronary interventions, admissions to hospital for heart failure). The authors assumed a constant probability of events over time, which is a conservative assumption; the occurrence of fewer events is favouring the ASA arm. As the authors indicated, these biases suggest a lower cost-effectiveness ratio (than the base case) for clopidogrel in each sub group. These findings indicate a benefit at disbursements that is within the realms of possibility, based on clear benefit for patients with peripheral vascular disease from the *CAPRIE* study. The clinical advantage and cost-effectiveness of clopidogrel in secondary prevention as determined in the study by Schleinitz et al. has been discussed controversially by Eriksson et al. [44].

Conclusion

Cost consciousness has become more and more important over the last years for different therapy options, especially in Europe.

In particular for clinicians running their own private practise economical efficacy of prescriptions came to the fore. On the other hand, there is the duty to give patients the best possible treatment. This, against the background of heavy ethical responsibility, which may put physicians into a conflicting situation, requires continuous cost-effectiveness studies in the future. The compendium of diverse health care systems justifies the use of clopidogrel in the accepted indications also from an economic point of view. This review supports the notion that clopidogrel has both a medical *and* an economic benefit. On the basis of a majority of the reviewed studies the use of clopidogrel is warranted and the range of costs-effectiveness ratios were well within the range of other accepted medical interventions. Nevertheless limitations of cost-effectiveness studies have to be taken in account before introducing new indications for drugs therapies.

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